© 2017 IJSRSET | Volume 3 | Issue 5 | Print ISSN: 2395-1990 | Online ISSN : 2394-4099
Themed Section: Science

Advances In the Development of New Quinazoline Based Anti-Cancer Agents

Jayanti S. Rajora
Department of Chemistry, Government Science College, Gandhinagar, Gujarat, India

ABSTRACT
The growing knowledge of cancer-related pathways has recently resulted in the discovery of some novel potential targets for therapy, with quinazolines receiving increasing attention as small molecular inhibitors.
The present paper covers a brief report of newer quinazoline based anti-cancer agents.
Keywords: Quinazolines, Anti-Cancer Activity.

I. INTRODUCTION

The search for new anticancer agents has been one of the most challenging tasks for the medicinal chemists. Discovery and development of anticancer agents are the key focus of several pharmaceutical companies as well as nonprofit government and non-government organizations.

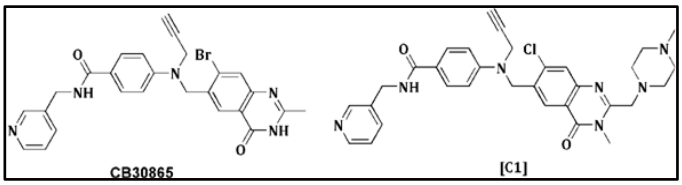
Quinazoline derivatives have received a great interest as anti-cancer agents since the discovery of Gefitinib. From about 1995 to 2006, the anticancer quinazolines panorama has been dominated by the 4-anilinoquinazolines as tyrosine kinase inhibitors [1]. Interests in quinazolines as anticancer agents have further increased after the discovery of thymidylate synthase inhibitors Raltitrexed and Thymitaq.

Past two decades have witnessed growth in the knowledge of cancer-related pathways and consequently novel anti-cancer agents targeting newer cancer-related pathways have been researched and developed.

II. 'IN VITRO' ANTI-CANCER ACTIVITY STUDIES OF QUINAZOLINES

Studies on Anti-cancer Activity of Quinazolines using specific cell-lines

V. Bavetsias et al. have reported design and synthesis of water-Soluble analogues of Quinazolin-4-one **CB30865** and tested them as inhibitors of human lymphoblastoid W1L2 cell growth [2]. The compound **[C1]** was found to be 6-fold more cytotoxic than CB30865 with W1L2 IC_{50} of 0.49 $\pm$ 0.24 nM [Figure-1].



[Figure-1]

Yang S. et al. have synthesized S'-substituted 4-alkyl(aryl)thioquinazoline derivatives and reported their anti-cancer activity against PC3 cells as well as against Bcap37 and BGC823 cells [3]. The compounds were found to be highly effective against PC3 cells but showed weak activity against Bcap37 and BGC823 cells.

P. Mani Chandrika et al. have reported anti-cancer activity of novel 4,6-disubstituted quinazoline derivatives against U937 leukemia cell lines [4]. Some of the compounds exhibited promising anti-cancer activity with reference to standard drug Etoposide.

R. Suthakaran et al. have reported anti-tumor activity of novel 4(3*H*)-Quinazolinones [5].

Saber El-Sayed Barakat et al. have reported the synthesis of novel series of quinazolinone derivatives 6–15 having the biologically active thioxo group. The compounds were tested for anti-tumor activity against Ehrlich Ascities Carcinoma cells [6]. However, the compounds did not show any significant anti-tumor activity against Ehrlich Ascities Carcinoma cells.

Alafeefy A. et al. have synthesized twenty-two novel quinazoline derivatives and examined their anti-tumour activity against three tumour cell lines, namely human breast cancer cell line (MCF-7), human cervical cancer cell line (HeLa) and human hepatoma cell line (HepG2) [7]. Twelve of the tested compounds have shown promising anti-tumour activity with an IC50range of 5.0–9.7 μg/mL.

N. Mulakayala et al. have reported anti-cancer activity of novel 2-aryl quinazolin-4(3H)-ones against human chronic myeloid leukemia cells (K562), human colon carcinoma cells (Colo-205), and human breast cancer cell line (MDA-Mb 231MR32) [8].

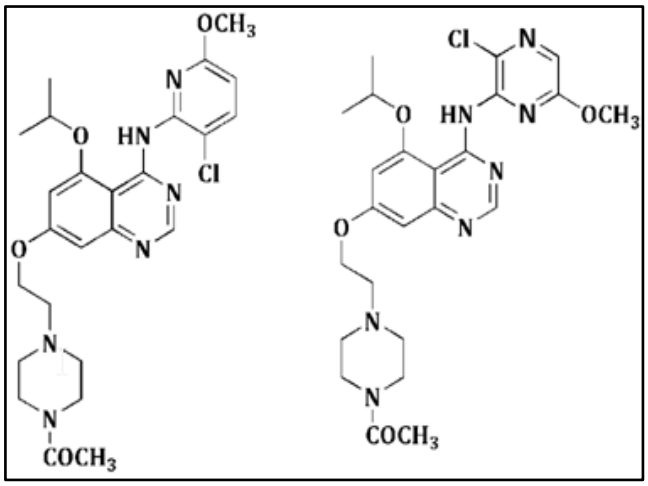
Hurmath U. et al. have reported in vitro anti-tumor activity of a series of 4-[2-(4-chlorobenzyl)-4-oxoquinazolin-3(4H)-yl)benzoyl] derivatives [9]. The in vitro anti-tumor studies were performed MTT assay against HeLa cell line.

Studies on Kinase Inhibitory Activity of Quinazolines

Smaill J. et al. have reported EGFR inhibitory activity of 4-Anilinoquinazoline- and 4-anilinopyrido[3,2-d]pyrimidine-6-acrylamides substituted with solubilizing 7-alkylamine or 7-alkoxyamine side chains [10]. The compounds were evaluated for their inhibition of phosphorylation of the isolated EGFR enzyme and for inhibition of EGF-stimulated autophosphorylation of EGFR in A431 cells and of heregulin-stimulated autophosphorylation of *erb*B2 in MDA-MB 453 cells. Quinazoline analogues with 7-alkoxyamine solubilizing groups were potent irreversible inhibitors of the isolated EGFR enzyme, with IC_{50} values from 2 to 4 μM, and potently inhibited both EGFR and *erb*B2 autophosphorylation in cells.

Wang Y. et al. have synthesized series of 4-anilinoquinazolines and evaluated them for their inhibitory activity against Src kinase using an ELISA assay [11].

Barlaam B. et al. have reported selective c-Src kinase inhibition by 4-(2-chloro-5-methoxyanilino)quinazolines bearing 4-heteroaryl substituents [12]. Two compounds of the series were found to be the most effective in a c-Src-driven cell proliferation assay [Figure-2].



[Figure-2]

Petrov K. et al. explored the SAR by synthetic modifications on a 6-furanylquinazoline scaffold to optimize the dual ErbB-1/ErbB-2 tyrosine kinase inhibition [13]. The results of SAR studies revealed that 4-(3-fluorobenzyloxy)-3-haloanilino provided

the best enzyme potency and cellular selectivity. The discovery of Lapatinib emerged from this work.

Lippa B. et al. have reported the synthesis and biological evaluation of 4-anilinoquinazoline chemotype based potent and selective inhibitors of the erbB2 kinase [14].

A novel series of (S)-1-acryloyl-N-[4-(arylamino)-7-(alkoxy)quinazolin-6-yl]pyrrolidine-2-carboxamides were synthesized and evaluated as Her-1/Her-2 dual inhibitors by Cha MY et al. [15]. Two compounds of the series demonstrated excellent EGFR inhibition activity even toward the T790M mutation of Her-1 tyrosine kinase with excellent selectivity. The results implied that both the compounds had the potential as novel therapeutic agents for EGFR-targeting treatment of solid tumors, especially Her-1 selective inhibitor-resistant non-small cell lung cancer.

Li Ri-Dong et al. designed and synthesized a novel series of EGFR inhibitors by combination of dithiocarbamic acid esters and 4-anilinoquinazolines [16]. SAR studies revealed that the substituents on C6 and C7 positions of quinazoline, the amine component of dithiocarbamate moiety and the linker greatly affected the activity.

4-anilinoquinazoline and 4-anilinoquinoline scaffolds bearing a 2,2,6,6-tetramethylpiperidine-N-oxyl were synthesized by Li S. et al. [17]. The compounds were evaluated for their ability to inhibit EGFR tyrosine kinase and A431 cell lines.

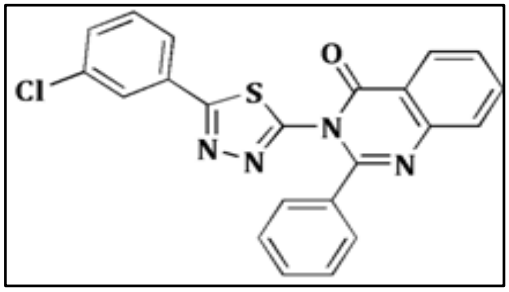
Zhang Y. et al. have reported EGFR inhibitory activity of 5,6,7-trimethoxy-N-phenyl(ethyl)-4-aminoquinazoline compounds [18].

Garofalo A. et al. designed and synthesized three series of 6,7-dimethoxyquinazoline derivatives substituted in the 4-position by aniline, N-methylaniline and aryloxy entities for targeting EGFR and VEGFR-2 tyrosine kinases [19]. The impact of the variation in the 4-position substitution of the quinazoline core was studied. Studies revealed that substitution by aryloxy groups led to new compounds which are selective inhibitors of VEGFR-2 enzyme with IC50 values in the nanomolar range *in vitro*.

III. '*IN VIVO*' ANTI-CANCER ACTIVITY STUDIES OF QUINAZOLINES

Govindraj Y. et al. have reported synthesis and in vivo anti-cancer screening of six novel 2-{[Bis-(2-chloroethyl) amino] methyl}-6, 8-dinitro-1-(4-substituted ethyl)-1H-quinazolin-4-one derivatives [20]. The compounds were evaluated for short-term in-vitro antitumor activity and then in-vivo anticancer activity by body weight analysis, mean survival time and percentage increase in life span methods in Swiss albino mice bearing DLA 1x106cells/ml.

Joseph A. et al. have synthesized 3-(1,3,4-thiadiazol-2-yl)-quinazolin-4-(3H)-ones as novel anti-cancer agents [21]. In vitro anticancer activity of all the synthesized compounds was determined by MTT assay on HeLa (Human cervical cancer cell) cells. Most active compounds found in vitro studies were further evaluated for their in vivo activity on Liquid tumor (Ehrlich's Ascites Carcinoma; EAC) induced mice. The anticancer activity of one compound was found to be comparable to that of cisplatin against HeLa cells and it was also effective in preventing the growth of tumor in mice as indicated by decrease in progressive gain in body weight as well as increase in life span when compared to animals of control group [Figure-3].

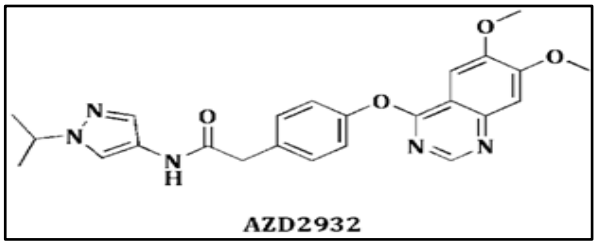


[Figure-3]

Das S. et al. have reported anti-cancer activity of 3-(arylideneamino)-phenyl quinazoline-4(3H)-ones [22].

The most potent cytotoxic compound identified from the *in vitro* studies was further tested *in vivo* and it was found that treatment with multiple doses of the compound significantly increased the survival rate of B16F10 tumor bearing BALB/c mice by suppressing the volume of tumor while decreasing microvascular density and mitotic index of the tumor cells.

Ple P. et al. have discovered a new molecule, **AZD2932** [Figure-4], which is a Quinazoline ether Inhibitor with high affinity for VEGFR-2 and PDGFR tyrosine kinases [23]. *In vitro* studies, pharmacokinetics and *in vivo* evaluations led to the selection of **AZD2932**.



[Figure-4]

The pharmacokinetic profile along with *in vitro* potency correlated with both PD and anti-tumor efficacy in the C6 model. Alongside on-going pre-clinicalevaluation, these data indicate that **AZD2932** has the potential to become an anti-angiogenic agent in the clinic, through the inhibition of PDGFR and VEGFR-2 signaling.

IV. QSAR STUDIES ON ANTI-CANCER QUINAZOLINES

Literature survey revealed that only few reports covering QSAR studies on anti-cancer quinazolines have been published.

The research group of Noolvi M. et al. has performed number of QSAR studies on kinase inhibitory activity of Quinazoline derivatives. Noolvi M. et al. have reported 2D-QSAR on a series of 4-anilinoquianzolines as tyrosine kinase (EGFR) inhibitors [24]. QSAR studies were performed on a set of 137 analogs of quinazoline using MDS vlife science QSAR plus module by using Multiple Linear Regression (MLR), Principal Component Regression (PCR) and Partial Least Squares (PLS) Regression methods. Among these, MLR method had shown a very promising result as compared to other two methods.

Noolvi M. et al. have also reported 3D-QSAR studies on a series of 4-anilino quinazoline derivatives using the k-Nearest Neighbor Molecular Field Analysis (kNN-MFA) approach [25]. 3D-QSAR method was used to study the correlation between the molecular properties and the tyrosine kinase (EGFR) inhibitory activities on a series of quinazoline derivatives using SW, SA and GA variable selection method.

A comparative QSAR of quinazoline derivatives acting as Protein tyrosine kinases (erbB-2) inhibitors have been also reported by Noolvi M. et al. [26]. The studies were performed using Multiple Linear Regression, Principal Component Regression and Partial Least Squares Regression methods. Among these three methods, Multiple Linear Regression (MLR) method was found to give very promising results as compared to other two methods.

Mirzaie S. et al. have reported 3DQSAR studies on multi-acting quinazoline derivatives as HER2 kinase inhibitors [27]. Self-Organizing Molecular Field Analysis (SOMFA), a grid-based and alignment-dependent 3D-QSAR method, was employed to study the correlation between the molecular properties and HER2 inhibitory potency of the quinazoline derivatives.

V. CONCLUSION

The quinazolines are potential candidates as anti-cancer agents given the success of clinically used new quinazoline-based drugs. Number of researchers have been working in search of newer and more effective quinazoline derivatives with higher anti-cancer activity. However, there is a need to focus more on SAR relationships and design of newer agents based on that data.

VI. REFERENCES

[1] Marzaro G, Guiotto A, Chilin A. Quinazoline derivatives as potential anticancer agents: a patent review (2007-2010). *Expert OpinTher Pat.*, 22, 223-252, 2012.

[2] V. Bavetsias et al. The Design and Synthesis of Water-Soluble Analogues of CB30865, a Quinazolin-4-one-Based Antitumor Agent.*J. Med. Chem.*, 45, 3692-3702, 2002.

[3] Yang S. et al. Synthesis and bioactivity of 4-alkyl(aryl)thioquinazoline derivatives. *Bioorg. Med. Chem. Lett.*, 17, 2193-2196, 2007.

[4] P. Mani Chandrika et al. Synthesis of novel 4,6-disubstituted quinazoline derivatives, their anti-inflammatory and anti-cancer activity (cytotoxic) against U937 leukemia cell lines. *Eur. J. Med. Chem.*, 43, 846-852, 2008.

[5] R. Suthakaran et al. Inflammation: Synthesis and pharmacological investigation of some new 4(3*H*)-Quinazolinone analogues as anti-oxidant, antihistaminic, anti-inflammatory and anti-tumor agents. *Rasayan J. Chem.*, 1, 263-275, 2008.9.

[6] Saber El-Sayed Barakat et al. Novel Quinazolinone Derivatives as Possible Antitumor Agents. *Phosphorus, Sulfur, and Silicon and the Related Elements*, 182, 65-77, 2007.

[7] Alafeefy A. et al. Design, synthesis and biological evaluation of novel quinazoline derivatives as potential anti-cancer agents. *Journal of enzyme inhibition and medicinal chemistry*, 27(4), 541-545, 2012.

[8] N. Mulakayala et al. $InCl_3$-catalysed synthesis of 2-aryl quinazolin-4(3*H*)-ones and 5-aryl pyrazolo[4,3-d]pyrimidin-7(6*H*)-ones and their evaluation as potential anticancer agents. *Bioorg. Med. Chem. Lett.*, 22, 5063-5066, 2012.

[9] Hurmath U. et al. Synthesis and in Vitro Anti Tumor Activity of Some Novel 2,3-Disubstituted Quinazolin 4(3H)-one Derivatives. *Journal of Applied Pharmaceutical Science*, 3 (10), 136-140, 2013.

[10] Smaill J. et al. Tyrosine Kinase Inhibitors. 17. Irreversible Inhibitors of the Epidermal Growth Factor Receptor: 4-(Phenylamino)quinazoline- and 4-(Phenyl amino)pyrido[3,2-d]pyrimidine-6-acrylamides Bearing Additional Solubilizing Functions. *J. Med. Chem.*, 43, 1380-1397, 2000.

[11] Wang Y. et al. Inhibitors of Src tyrosine kinase: the preparation and structure–activity relationship of 4-anilino-3-cyanoquinolines and 4-anilinoquinazolines. *Bioorg. Med. Chem. Lett.*, 10, 2477-2480, 2000.

[12] Barlaam B. et al. New heterocyclic analogues of 4-(2-chloro-5-methoxyanilino) quinazolines as potent and selective c-Src kinase inhibitors. *Bioorg. Med. Chem. Lett.*, 15, 5446-5449, 2005.

[13] Petrov K. et al. Optimization and SAR for dual ErbB-1/ErbB-2 tyrosine kinase inhibition in the 6-furanylquinazoline series. *Bioorg. Med. Chem. Lett.*, 16, 4686-4691, 2006.

[14] Lippa B. et al. The discovery of highly selective erbB2 (Her2) inhibitors for the treatment of cancer. *Bioorg. Med. Chem. Lett.*, 17, 3081-3087, 2007.

[15] Cha MY et al. Discovery of A Novel Her-1/Her-2 Dual Tyrosine Kinase Inhibitor for the Treatment of Her-1 Selective Inhibitor-Resistant Non-small Cell Lung Cancer. *J. Med. Chem.*, 52, 6880-6888, 2009.

[16] Li Ri-Dong et al. Novel EGFR inhibitors prepared by combination of dithiocarbamicacid esters and 4-anilinoquinazolines. *Bioorg. Med. Chem. Lett.*, 21, 3637-3640, 2011.

[17] Li S. et al. Synthesis and biological evaluation of quinazoline and quinoline bearing 2,2,6,6-tetramethylpiperidine-N-oxyl as potential epidermal growth factor receptor(EGFR) tyrosine kinase inhibitors and EPR bio-probe agents. *Eur. J. Med. Chem.*, 65, 271-278, 2012.

[18] Zhang Y. et al. Synthesis and anticancer activities of 5,6,7-trimethoxy-N-phenyl(ethyl)-

4-aminoquinazoline derivatives. *Eur. J. Med. Chem.*, 66, 335-344, 2013.

[19] Garofalo A. et al. Impact of aryloxy-linked quinazolines: A novel series of selective VEGFR-2 receptor tyrosine kinase inhibitors. *Bioorg. Med. Chem. Lett.*, 21, 2106-2112, 2011.

[20] Govindraj Y. et al. Synthesis and In-vivo Anticancer Screening of 2-{[Bis-(2-Chloroethyl)Amino]Methyl}-6,8-Dinitro-1-(4-Substituted Ethyl)-1h-quinazolin-4-One Derivatives. *Academic Journal of Cancer Research*, 2(2), 73-77, 2009.

[21] Joseph A. et al. Synthesis and anticancer activity of some novel 3-(1,3,4-thiadiazol-2-yl)-quinazolin-4-(3H)-ones. *Orbital-The Electronic Journal of Chemistry*, 2(2), 158-167, 2010.

[22] Das S. et al. Anticancer Potential of 3-(Arylideneamino)-2- Phenylquinazoline-4(3H)-One Derivatives. *Cell Physiol. Biochem.*, 29, 251-260, 2012.

[23] Ple P. et al. Discovery of AZD2932, a new Quinazoline Ether Inhibitor with high affinity for VEGFR-2 and PDGFR tyrosine kinases. *Bioorg. Med. Chem. Lett.*, 22, 262-266, 2012.

[24] Noolvi M. et al. 2D QSAR Studies on a Series of Quinazoline Derivatives as Tyrosine Kinase (EGFR) Inhibitor: An Approach to Design Anticancer Agents. *Letters in Drug Design & Discovery*, 7, 56-586, 2010.

[25] Noolvi M. et al. 3D QSAR Studies on a Series of 4-Anilino Quinazoline Derivatives as Tyrosine Kinase (EGFR) Inhibitor: The k-Nearest Neighbor Molecular Field Analysis Approach. *International Journal of Drug Design and Discovery*, 1, 298-309, 2010.

[26] Noolvi M. et al. A Comparative QSAR Analysis of Quinazoline Analogues as Tyrosine Kinase (erbB-2) Inhibitors. *Medicinal Chemistry*, 7, 200-212, 2011.

[27] Mirzaie S. et al. Combined 3D-QSAR modeling and molecular docking study on multi-acting quinazoline derivatives as HER2 kinase inhibitors. EXCLI, 12, 130-142, 2013.